REMARKS

Claims 1-11 and 13-14 are pending in this application and have been rejected by the Examiner. Claim 12 has previously been cancelled. Claims 15-30 have been cancelled to remove the non-elected invention. Claims 1 and 11 have been amended to add "C_{1-4}alkyl ester" in front of the term "prodrug". Support for such amendment may be found on Page 5, paragraph [0105] of the published specification (2006/0058349). Claims 1 and 14 have been amended to further clarify the claims by adding the (R) and (S) notation to the chemical structures. This notation is inherent in the structures as drawn in the original and current claims. Such notation can also be found in the examples in the specification. Claim 1 has also been amended to add a dash in front of "alkylAr^1" so as to read "-alkylAr^1". The amendment is to correct an obvious mistake as it can be seen in the examples that Applicants intended for the ring-nitrogen to be substituted with alkylaryl wherein the substituent is connected via the alkyl group. The claims have also been amended to correct typographical errors. It is believed no new matter has been added.

Restriction Requirement

Previously, the Examiner restricted the claims thirteen ways for lack of unity of invention, arguing that U.S. Patent 4,639,436 (Junge et al.) anticipates the claimed compounds of Group I. *Office Action* dated 7/29/2008, p. 4. The Examiner now made the restriction requirement final. Without agreeing as to the accuracy of the Examiner's statement, Applicants cancelled non-elected claims 15-30 with traverse, reserving the rights to pursue cancelled subject matter in a divisional and/or continuation application.

Rejection under 35 *U.S.C.* § 112, Second Paragraph

The Examiner maintained the rejections of claims 1-10 and 13-14 for being indefinite. The Examiner argued that the structural formula of the compounds of the current invention uses the dotted ("----") and the wedged ("▬") configurations, which allegedly denotes the up and down configuration from the ring, rather than the well recognized "*R*" and "*S*" configuration and therefore does not limit the claimed compounds to a specific stereochemistry. *Office Action* dated

12/11/2009, p. 2-3 and *Office Action* dated 6/4/2009, ¶ 3. The Examiner concluded that the claims are without stereo limitations and as such are indefinite. *Id.*

To avoid any doubt and to expedite allowance of the claims, Applicants have amended claims 1 and 14 to specify the stereochemistry of each chiral carbon on the ring of the claimed compounds. It is believed that the amendment will overcome the Examiner's rejection under section 112, second paragraph. Withdrawal of the rejections under section 112, second paragraph is earnestly requested.

Rejection under 35 *U.S.C.* § 112, First Paragraph

The Examiner maintained the rejection of claims 1-11 and 13-14 for failing to comply with the enablement requirement, arguing that the specification does not provide "sufficient information as to what kind of modification of the drug functional groups to provide an inactive prodrug which will be released into the active form in vivo." *Office Action* dated 6/4/2009.

Applicants have amended claim 1 to add "C_{1-4}alkyl ester" in front of the term "prodrug" in claims 1 and 11. Applicants respectfully submit that the specification is enabling for such prodrugs of the claimed compounds as one skilled in the art would know what prodrugs are possible, e.g., for the hydroxy substituents and how to make such prodrugs so as to allow a skilled artisan to make and use the invention. As such, C_{1-4}alkyl esters formed with the claimed compounds of the invention, for example, wherein the hydroxy substituent of the compound of the invention (e.g., drug-OH) forms an alkyl ester with the hydroxy substituent (e.g., drug-O-**C(O)-C_{1-4}alkyl**) are enabled by the invention.

The Examiner argued that various esters of the compounds disclosed in Table 1 of U.S. Pat. No. 5,003,072 (the '072 Patent) have biological activities, and as such, the acylated claimed compounds are not "inactive" prodrugs. Applicants respectfully disagree. None of the Examples disclosed in the '072 Patent falls under the scopes of the claimed invention as they do not have aryl or -alkylaryl substituents on the ring-nitrogen nor do they have the same stereochemical configuration as the currently claimed compounds. It is improper to impute the activities of the compounds of the '072 patent onto the compounds of the current invention on the basis that they are all polyhydroxylated azasugar compounds without consideration of the stereochemistry and side chains of the compounds. As such, the Examiner has not shown that the claimed prodrugs of

the compounds of the invention have biological activities. Even if the corresponding ester (or acylated) compounds of the current invention are biologically active, Applicants respectfully submit this does not necessarily render them unfit as a prodrug. In an article in the *Mini-Reviews in Medicinal Chemistry*, a journal designed for medicinal and pharmaceutical chemists, prodrug is defined as "being inactive or much less active than the drug and must be hydrolyzed by chemical or enzymatic means, releasing the active molecule." Silva et al., "Advances in Prodrug Design", *Mini-Reviews in Medicinal Chemistry*, 2005, 5:893-914, 895, second column (emphasis added) (submitted herewith). In another article, *J. Med. Chem.*, 2007, 50(15):3743-3746, the authors discuss the synthesis and biological activity of a Gemcitabine phasphoramidate prodrug, noting that "the prodrug was about an order of magnitude less active than gemcitabine against wild-type cells ", but "[t]he prodrug was more active than gemcitabine against two deoxycytidine kinase-deficient cell lines." *Id.* at abstract (submitted herewith). These articles, therefore, support Applicants' position that just because a compound has some biological activities does not render it unfit for a prodrug. Therefore, whether the prodrugs of the claimed compounds have biological activities or not would not necessarily disqualify them as prodrugs. Applicants respectfully request the Examiner to reconsider and withdraw the rejection under Section 112, First Paragraph.

Rejection under 35 *U.S.C.* § 102(b)

The Examiner maintained the rejection of claims 1-11 and 13-14 for being anticipated by Boeshagen et al. CA 113:126581; Ezure et al. CA 116:236093, RN 141206-38-4; Broek et al. CA 119:96007, RN 149302-52-3, RN 149302-53-4; Berg et al. RN 8117-43-3; Kurihara et al. CA 114:185939 RN 1333342-47-9, under 35 *U.S.C.* § 102(b) based on the conclusion that the claimed compounds do not contain any stereo limitation. *Office Action* dated 6/4/2009, p. 4.

Applicants have amended the claims to add the (R) and (S) notation and therefore should overcome the rejection under section 102 as Boeschagen et al., CA 113:126581; Broek et al., CA 119:96007; Kurihara et al., CA 114:185939 and Berg et al., CA 96:117597 (the search results cited by the Examiner) all disclose compounds having a (2R, 3R, 4R, 5S) configuration, and Ezure et al., CA 116:236093 discloses compounds having a (2R, 3S, 4R, 5S) configuration, all of which differ from the (2S, 3R, 4R, 5S) compound of the claimed invention. Because art cited by the Examiner

do not disclose a compound having the stereo configuration and the ring-nitrogen substituents as the claimed invention, they fail to be anticipatory. Reconsideration and withdrawal of the rejections under Section 102 are respectfully requested.

Rejection under 35 *U.S.C.* § 103

The Examiner maintained the rejection of claims 1-11 and 13-14 under 35 *U.S.C.* § 103(a) as allegedly being obvious over Boshagen et al., U.S. 5,051,407 (the '407 Patent) or Jacob et al., U.S. Pat. 6,225,325 (the '325 Patent) in view of Greene, arguing that the claimed compounds are not limited by the stereo configuration because the "S" and "R" notation was not used. *Office Action* dated 6/4/2009, page 4, ¶ 6. The Examiner noted that if "the claimed compounds are demarcated from the prior art variation, then such difference can be considered." *Id.*

Here, Applicants have amended the claims to further clarify the stereochemistry of the compounds of the invention to be the (2S, 3R, 4R, 5S) configuration and earnestly request reconsideration and withdrawal of the rejections. Applicants add that while the art references cited by the Examiner disclose various stereoisomers of azasugar compounds, they do not disclose or suggest a compound having a (2S, 3R, 4R, 5S) configuration as the lead compound. If anything, the '047 Patent discloses DNJ (2R, 3R, 4R, 5S) derivatives as the lead compounds as they are specifically exemplified and are shown to have antiviral activities. *See* U.S. 5,051,407, Column 12, Table 1. Similarly, the '325 Patent, while discloses "certain iminosugar glucosylceramide synthase inhibitors" useful for treating multidrug resistance in a patient undergoing chemotherapy, identifies glucitol (2R, 3R, 4R, 5S) and galacitol (2R, 3S, 4R, 5S) compounds as the lead compounds for the invention as those compounds are preferred and specifically exemplified and claimed. *See* U.S. 6,225,325, Column 3, lines 60-65, Column 4, lines 47-55, and claim 1-42. Again, the '005 Patent discloses various stereoisomers of azasugars as inhibitors of Hepatitis C virus (HCV) p7 protein, but identifies n-nonyl, 7-oxanonyl or 10-oxaundecyl DNJ (2R, 3R, 4R, 5S) and DGJ (2R, 3S, 4R, 5S) compounds and their isomers as the most preferred compounds. *See* U.S. 7,256,005, Column 9, lines 41-54. The Examiner has not identified any suggestion in the art as to why a skilled artisan would pick the (2S, 3R, 4R, 5S) or the –alkylaryl or aryl substituted azasugar as the lead compound other than the disclosure in the cited art that azasugars are

identified as a class of compounds with biological activities. This teaching would not render the claimed invention obvious as such general teaching is in stark contrast to the Federal Circuit's lead compound identification requirement, stating that "post-KSR, a prima facie case of obviousness for a chemical compound still, in general begins with the reasoned identification of a lead compound". *Eisai Co. v. Dr. Reddy's Lab.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008), Similarly in *Takeda Chem. Industries, Ltd. V. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), the Federal Circuit specifically states that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure" *Id.* at 1356. The Court went on to clarify: "[a] known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.' [(citation omitted).] We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required.'." *Id.* (citations omitted). Here, a general teaching that azasugar is a known class of glucosidase inhibitors would not render the Ar^1 or $-alkylAr^1$ substituted (2S, 3R, 4R, 5S) compounds obvious.

The Examiner's argued that the prior art evidences that "variation of stereo structure of the piperidine core would not affect the activity and are alternative choices for such compounds (see especially, U.S. 7,250,005) and Kato et al. disclosed the same expectation that all enantiomers are biologically active while some may be more active or selective than others against specific enzymes." *Office Action* dated 6/4/2009, p. 5. Applicants respectfully disagree. The Examiner's contention is in direct contradiction with the disclosure of Kato et al. In looking at Kato et al., which Applicants again assert that the publication is not prior art to the current application as it was published in 2004, after Applicants' PCT filing on July 17, 2003[1], one skilled in the art would not conclude that one stereo isomer can be an alternative choice for another. For instance, Tables 2 and 3 shows that L-*ido*-DNJ and L-*manno*-DNJ are not active against any enzyme at all and would

[1] Even though Kato et al. cited references that predate the current application, the rest of the contents of Kato et al. disclosing specific biological activities are nevertheless not prior-art to the current application.

not be an alternative choice for D-*manno*-DNJ or D-*ido*-DNJ as one isomer has inhibitory activities against specific glycosidases while the other isomer does or may not have inhibitory activities at all. As previously argued, in looking at *Kato et al.*, it is difficult to rationalize, in hindsight, the inhibitory activities of the various enantiomers of imino sugar compounds, let alone predict the activity of an enantiomer against a particular enzyme. This unpredictability of activities is also seen in the compounds of the invention. For instance, Table 1 of the current specification shows that, in addition to GCS activities, the compounds of the current invention also inhibits non-lysosomal-β-glucocerebrosidase, which activities are useful for, e.g., reversibly rending a male mammal infertile as shown in Yildiz et al., "Mutation of β-glucosidase 2 causes glycolipid storage disease and impaired male fertility", *J. Clinical Investigation*, 2006, 116:2985-2994 (submitted herewith). Therefore, given the unpredictability of activities of sugar and sugar mimetic compounds, one skilled in the art would not expect that all of the stereoisomers are active against a certain enzyme and therefore would not be motivated modify the prior art compounds and still have an expectation of success. Accordingly, the Examiner has failed to show where or how the cited art identified the (2S, 3R, 4R, 5S) as the lead compound or why one skilled in the art would make the change in the prior art compound so as to arrive at the claimed invention. Only with impermissible hindsight knowledge of the current application is the Examiner able to identify the (2S, 3R, 4R, 5S) compound as a compound of choice. Applicants respectfully submit that the Examiner has not met her burden of proving a prima-facie case of obviousness. For the reasons stated herewith, Applicants earnestly request reconsideration and withdrawal of the rejections under 35 U.S.C. 103(a).

Provisional Obviousness Type Double Patenting Rejection

The Examiner maintained the rejection of claims 1-11 and 13-14 on the ground that the claims of the present invention are allegedly unpatenable over the claims of copending Application No. 10/522,207 (hereinafter "the '207 Application) or 10/586,188 (hereinafter "the '188 Application) in view of U.S. Patent No. 5,051,407, U.S. Patent No. 7,256,005 ('005) and Kato et al. as being barred by the non-statutory obviousness-type double patenting.

In view of the current amendment to the claims, adding the (R) and (S) notation to the

formulas, clearly distinguishing the currently claimed invention from the claims of the '207 and the '188 Applications, which are directed to azasugar derivatives having stereochemical configurations which are different from the compounds of formula (I) of the present invention, Applicants respectfully request reconsideration and withdrawal of the provisional obviousness-type double patenting rejections. Applicants again note that there is nothing predictable about the biological activities of chiral compounds as can be seen in Kato et al. since one stereo isomer of the azasugar may be significantly more selective against a specific therapeutic activity than another isomer of that compound or one isomer is active while the other is not at all. Accordingly, the disclosure of activity and/or toxicity of one stereoisomeric compound would not render obvious the activity and/or toxicity of the other stereoisomer. Therefore, the claimed compounds of the current invention are unobvious and patentably distinct from those claimed in the '208 and the '188 Applications. As such, Applicants respectfully request the withdrawal of the obviousness-type double patenting rejection.

Applicants further note that the later filed case ('188 Application) has not even been substantively examined yet, let alone issued as a patent nor have the claims been allowed in this case nor in the '207 case. As none of these applications have allowable claims, Applicants respectfully submit that the obviousness-type double patenting rejection is premature and respectfully requested that this rejection be addressed upon allowance of claims in at least one of the applications.

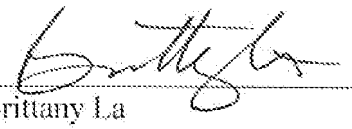
CONCLUSION

In summary, compounds of different stereochemistry, particularly sugars and sugar mimetics, may have completely different binding and/or biological activities as can be seen in Kato et al. The teaching of one stereoisomer as being biologically active would deter rather than motivate one skilled in the art to synthesize the other isomer, as there is no reason to expect the other compound to have the same activity, selectivity, and/or toxicity profile. Therefore, Applicants respectfully request that rejections of the pending claims be withdrawn.

As this response is filed within two-months from the mailing date of the Final Office Action dated June 4, 2009, which response is due September 4, 2009, it is believed no fee is

required. Should this be incorrect, the Commissioner is authorized to charge any additional fees, or credit any overpayment, to deposit account No. 50-4255.

Respectfully submitted,

Date August 4, 2009 By 

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